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MACROCYCLE FORMATION USING INTRAMOLECULAR DIELS ALDER REACTIONS: AN APPROACH TO 'CARBOCYCLIC' CYTOCHALASANS

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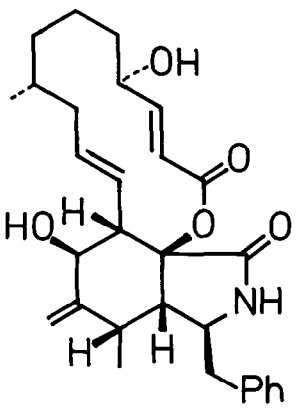
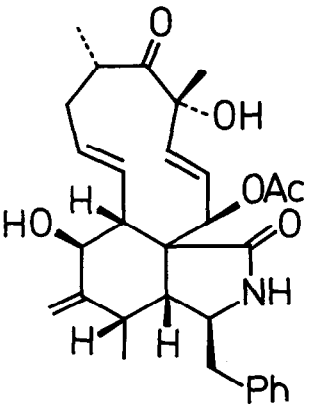
Abstract: The long-chain dienyl-pyrrolinone (17) cyclizes stereoselectively on heating to 120° for 17 h, or under high pressure, 11-13 kbar, 40° for 20 h, to give the macrocyclic products (18) and (20) in modest yield.

The cytochalasans, e.g. B(1) and D(2), and the chaetoglobosins, e.g. A(3), form an interesting group of biologically active natural products.[1,2] Considerable activity has been directed towards developing total syntheses of these compounds, the first synthesis, of cytochalasan B(1), being reported by Stork in 1978.[3] For several years we have been developing a convergent approach to cytochalasan synthesis which uses an intramolecular Diels Alder reaction to close the macrocyclic ring.[4] More recently we have been examining methods of applying this strategy to the 'carbocyclic' cytochalasans, e.g. D(2), and the chaetoglobosins. The recent publication by Stork,[5] of a total synthesis of cytochalasan B using such an intramolecular Diels Alder reaction, prompts us to describe some of our preliminary results in this area.



(1)



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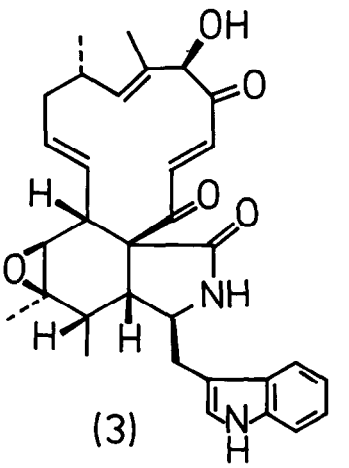
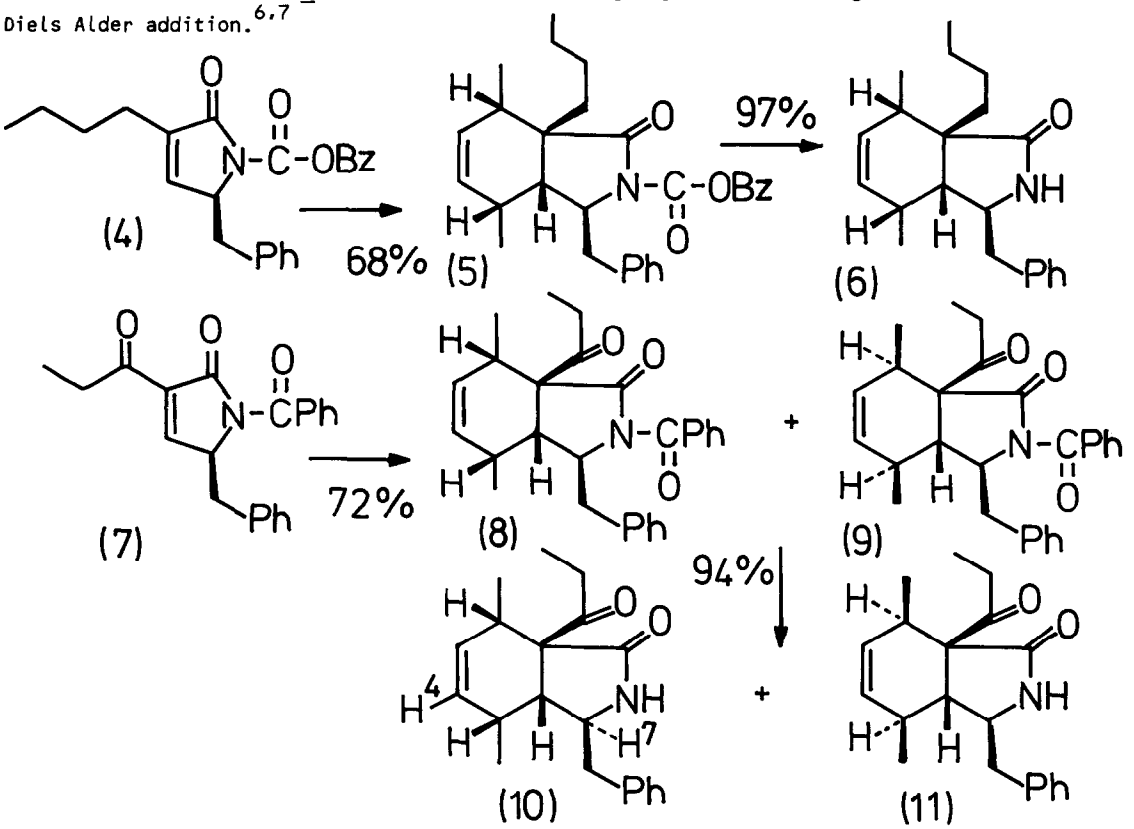


(3)

As preparatory work for this project the 3-substituted pyrrolinones (4) and (7) were prepared and heated with (2E,4E)-2,4-hexadiene.[6] † In both cases good yields of the desired Diels Alder adducts were obtained which could be deprotected to give isoindolones (6), (10), and (11). The 3-alkylpyrrolinone (4) reacted quite stereoselectively, only the

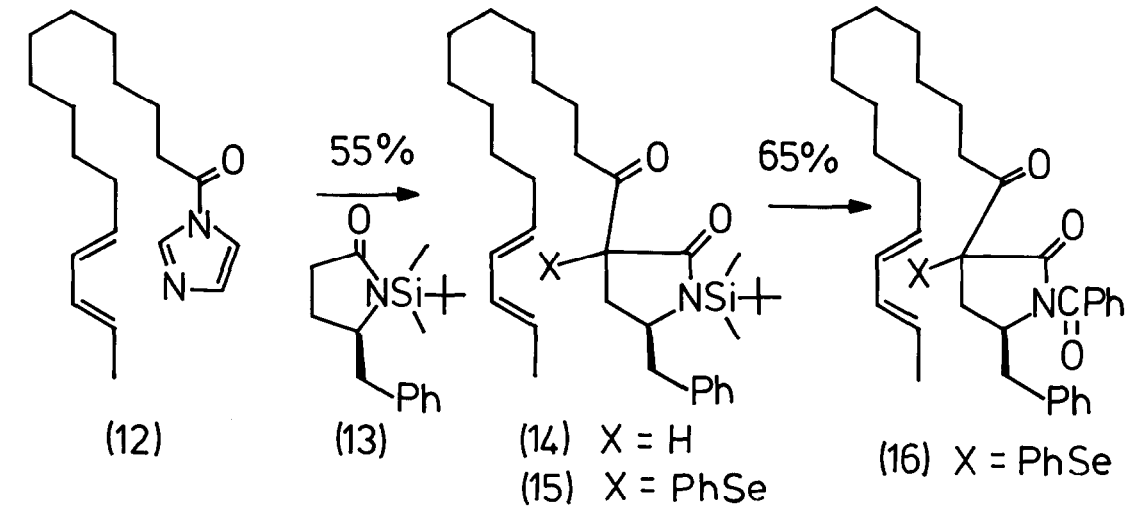
† New compounds were characterised spectroscopically together with analytical or accurate mass data.

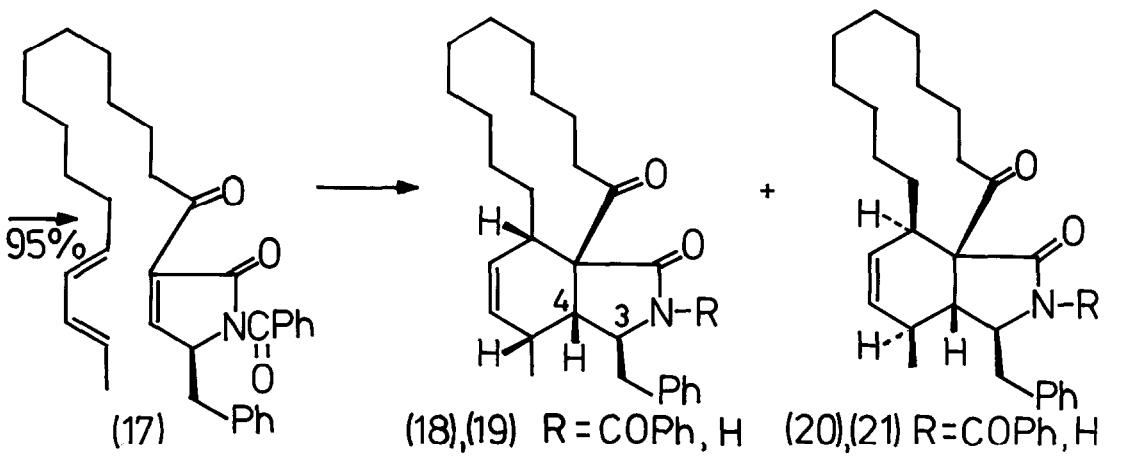
endo-isomer (5) being isolated, but vigorous reaction conditions were required (200°C, 36 h). The 3-ketopyrrolinone (7) was more reactive, a good yield of cycloadduct being obtained after 8 h at 105°C, but in this case a mixture of isomeric adducts (8) and (9) was formed. This mixture was not separated but was deprotected to give the separable isoindolones (10) and (11), ratio 85:15. The stereochemistry of the major product (10) was established by the observation of a significant (> 3%) nuclear Overhauser enhancement of the vinylic proton, H(4), on irradiation of the methine proton, H (7), and corresponds to the stereochemistry required for a cytochalasan synthesis. It would appear that the imide carbonyl group dominates the endo-exo selectivity. It was necessary to use N-acylpyrrolinones in these reactions, the analogous N-benzylpyrrolinones undergoing double bond migration rather than Diels Alder addition.[6,7]



Next the use of these Diels Alder reactions for macrocycle formation was studied. Thus the N-silylated pyrrolidinone (13) was acylated to give the 3-ketopyrrolidinone (14) which was phenylselenenylated using LDA/PhSeCl. The N-silyl group was then replaced by a benzoyl group (PhCOCl, benzene),[8] and the Diels Alder precursor (17) generated by oxidative-elimination of the phenylselenenyl moiety. The 3-acyl-pyrrolinone (17) so obtained was isolated but not purified, and its cyclization was studied under both thermal and high pressure conditions. It was found that an approximately 10% yield of an 85:15 mixture of cyclized products (18)and(20) was isolated after a 0.002 M solution of pyrrolinone (17) was heated in a Carius tube for 17 h at 120°C. Better yields, 20-30%, were obtained using high pressure conditions, 11-13 kbar, 20 h at 40°C. The N-acylated products were then

deprotected to give the macrocyclic pyrrolidinones (19) and (21) which were separated by chromatography.





The regioselectivity of this intramolecular Diels Alder reaction was established by ^{1}H n.m.r. spin decoupling of the allylic protons. The stereochemistry of the adducts was assigned by analogy with the intermolecular Diels Alder products discussed above, and this assignment for the major adduct (18) was consistent with the 4 Hz coupling observed between the bridgehead proton H(4), and the methine proton, H(3) (cytochalasan numbering).

Further work is in progress to develop a total synthesis of cytochalasin D(2), and the chaetoglobosins, using an intramolecular Diels Alder reaction to form the macrocyclic ring.

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